DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Matthew Lupo, Manager
Bristol-Myers Squibb
US Law & Promotion Integrity
777 Scudders Mill Road
Plainsboro, NJ 08536

RE: NDA # 022065
Ixempra® (ixabepilone)
MA # 247

Dear Mr. Lupo,

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) has reviewed the sales aid titled "Monotherapy/Combination Therapy Sales Aid 3" (691US10VC01407) for Ixempra® (ixabepilone) (Ixempra) submitted by Bristol-Myers Squibb (BMS) under cover of Form FDA 2253. This sales aid is misleading because it contains unsubstantiated efficacy claims and broadens the indication for Ixempra. Thus, the sales aid misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1(e)(6)(i), (xiv); (e)(7)(i) & (iii).

Background

Below are the indications and summary of the most serious and common risks associated with the use of Ixempra.[1] According to its FDA-approved prescribing information (PI), Ixempra is indicated:

> In combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.
>
> As monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.

Ixempra is associated with a number of serious risks, as detailed in the BOXED WARNING, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI. According to the BOXED WARNING, Ixempra, in combination with capecitabine, is contraindicated in patients with hepatic impairment due to increased risk of toxicity and neutropenia-related death. The PI also includes WARNINGS AND PRECAUTIONS for Ixempra regarding peripheral neuropathy (primarily sensory), myelosuppression, use in

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

patients with hepatic impairment, hypersensitivity reactions, cardiac adverse reactions (myocardial ischemia and ventricular dysfunction), potential for cognitive impairment from dehydrated alcohol USP excipient, and risk of fetal harm. The most common ADVERSE REACTIONS associated with Ixempra include peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. In combination with capecitabine, additional common ADVERSE REACTIONS included palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. Drug-associated hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

Unsubstantiated Efficacy Claims

Promotional materials are false or misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The sales aid presents numerous claims that overstate the efficacy of Ixempra. Specifically, pages five and 11 of the sales aid, which discuss the pivotal studies for Ixempra's monotherapy and combination therapy indications, respectively, make claims regarding stable disease, stable disease ≥6 months, and progressive disease. These efficacy claims are misleading as they are not supported by substantial evidence or substantial clinical experience. According to the CLINICAL STUDIES section of the Ixempra PI, the primary endpoint of the combination therapy study was progression-free survival (PFS). In the monotherapy study, the primary endpoint was overall response rate (ORR), comprised of complete response (CR) + partial response (PR). We note that stable disease, stable disease ≥6 months, and progressive disease were not pre-specified endpoints in the pivotal studies for Ixempra's monotherapy and combination therapy indications. Therefore, the pivotal studies do not provide substantial evidence to support these efficacy claims. We note pages five and 11 of the sales aid include the statement, "[s]table disease was a pre-specified analysis, not a pre-specified end point;" however, this statement does not mitigate the misleading implications made by the promotional claims in the sales aid. The FDA does not consider stable disease to be a valid endpoint for the measurement of response in these patients because it may reflect, in part, the natural history of the disease rather than any effect of the drug.[2]

Page 14 of the sales aid contains a bar graph, titled "Study 046: ORR within the pre-specified analysis of 1st line patients,[3]" that depicts ORR for patients who had relapsed ≤ 12 months after anthracyclines and taxanes in the adjuvant or neoadjuvant setting. The graph reports an ORR for patients in the Ixempra + capecitabine group of 68%, compared to an ORR of 17% for patients in the capecitabine group alone. The page also reports median PFS for this subset of patients (6.9 months for Ixempra + capecitabine compared to 2.7 months for capecitabine alone). Similarly, page 15 of the sales aid contains a bar graph, titled "Study

[2] Pazdur, R. Endpoints for Assessing Drug Activity in Clinical Trials**.** *The Oncologist.* 2008;13(suppl 2):19–21.
[3] Vahdat L, Fein LE, Karwal MW, et al. Ixabepilone plus capecitabine vs capecitabine in patients with metastatic breast cancer receiving ixabepilone in the first line setting: a pooled analysis from two phase lll studies. Poster presented at the San Antonio Breast Cancer Symposium. Dec. 12, 2008. Poster Number 6117.

046: ORR within the pre-specified triple-negative subgroup,[3]" which reports a 35% ORR for patients in the Ixempra + capecitabine group compared to an 11% ORR for patients in the capecitabine group alone. Finally, page 16 of the sales aid includes a bar graph, titled "Study 046: PFS within the pre-specified triple-negative subgroup,[3]" which reports a median PFS of 4.1 months for patients in the Ixempra + capecitabine group compared to a 1.6 month median PFS for patients in the capecitabine alone group. These presentations are misleading because they present the results of retrospective subgroup analyses performed using pooled sets of clinical data collected from multiple trials with differing clinical endpoints. In support of these claims, the sales aid references two poster presentations from the 2008 San Antonio Breast Cancer Symposium. Efficacy claims based on subgroup analyses of secondary end points from combined clinical studies, such as those found in the referenced poster presentations, do not constitute substantial evidence to support efficacy claims. These claims misleadingly suggest an improvement in ORR or PFS in first line therapy or in the triple negative subgroup of breast cancer patients when this has not been demonstrated by substantial evidence or substantial clinical experience. If you have data to support these claims, please submit them to FDA for review.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The front cover of the sales aid makes the following misleading presentation (emphasis original):

> **In MBC patients** who have progressed on an anthracycline and a taxane, with or without capecitabine
>
> ## What do you do after the taxane fails?

The claim "what do you do after the taxane fails?," which appears throughout the sales aid, misleadingly broadens the indication for Ixempra by suggesting that prior therapy with capecitabine is optional for all of the indicated uses, when this is not the case. According to the PI, patients must have failed prior treatment with a taxane, an anthracycline, **and** capecitabine in order to receive single-agent Ixempra. We acknowledge that Ixempra's full indication is presented at the bottom of the cover of the sales aid; however, this does not mitigate the misleading impression that Ixempra may be given as monotherapy without first having failed treatment with capecitabine.

[3] Rugo HS, Roche H, Thomas E, et al. Ixabepilone plus capecitabine vs capecitabine in patients with triple negative tumors: a pooled analysis of patients from two large phase III clinical studies. Poster presented at the San Antonio Breast Cancer Symposium. Dec. 12, 2008. Poster Number 3057.

Conclusion and Requested Action

For the reasons discussed above, this sales aid misbrands Ixempra by making unsubstantiated efficacy claims and broadening its indication in violation of the FD&C Act, 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1(e)(6)(i), (xiv); (e)(7)(i) & (iii).

OPDP requests that BMS immediately cease the dissemination of violative promotional materials for Ixempra such as those described above. Please submit a written response to this letter on or before July 16, 2012 stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Ixempra that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Ixempra comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Marybeth Toscano, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

Karen Rulli, Ph.D
Team Leader
Division of Professional Drug Promotion
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/s/

MARYBETH TOSCANO
06/29/2012

KAREN R RULLI
06/29/2012